

**Epigenetics Review and Synthesis: Autism Spectrum Disorder, Postpartum Depression, and
Posttraumatic Stress Disorder**

An Honors Thesis (PSYS 499)

by

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Epigenetics Review and Synthesis: Autism Spectrum Disorder, Postpartum Depression, and Posttraumatic Stress Disorder

As human characteristics emerge due to the interaction of genetic and non-genetic factors within a person's life, DNA is not the sole determinant of genetic expression (Moore, 2015). Understanding how genetic factors and environmental experiences interact to alter basic brain function and emotional behavior is essential to understanding how psychiatric disorders arise so as to develop clinical interventions. The current review explores epigenetics—the way in which the environment influences genetic expression—to examine the crucial role the environment plays in mediating genetic effects on behavior. Specifically, this paper examines epigenetics with respect to three different mental disorders: autism spectrum disorder (ASD), postpartum depression (PPD), and posttraumatic stress disorder (PTSD). The purpose of this review is to justify the need to study epigenetics and to propose ideas for future areas of research within the field.

Background

First introduced in 1874 by Sir Francis Galton, the idea of nature versus nurture has been popular among researchers (Badcock, 2015). Nature is everything one brings with oneself into the world while nurture is every influence that impacts one after birth. Galton's ideas were at the root of psychological research and theory for decades though they were never scientifically validated (McLafferty, 2006). Galton's ideas assume that either nature or nurture is the only force that makes us who we are and that this reigns true for every human trait. The nature versus nurture debate is no longer relevant as scientists now understand both genetic and situational factors work together in the development of human traits (Moore, 2015). This idea has become increasingly popular as researchers have begun to focus much research on gene x environment

(GxE) interactions, acknowledging that both genes and environment are important (Dick, 2011). According to Moore, people's physical and psychological traits are the product of interactions between biological molecules and their context. Moore states, "The conclusion that developmental circumstances— 'nurture'—can influence how a person's genome functions does not mean that the 'nature' is any less important than previously thought. But it does mean that DNA cannot specify destiny" (p. 16).

Completed in 2003, the Human Genome Project provided a new understanding of the genetic basis behind physiology and behavior (Masterpasqua, 2009). The term human genome refers to all the genetic information within the human body, stored in the DNA within each cell (Peters, Djurdjinovic, & Baker, 1999). The project identified 25,000 genes in each human cell (Masterpasqua). The sequences in each gene work together, constituting the blueprint for all human biological functions. This raises the question of the relationship between genotype (genetic sequence) and phenotype (genetic expression). According to Peters, Djurdjinovic, and Baker, DNA is the basis of who we are as the genetic makeup is unique per individual. As a result, "genetic information can be an important factor in defining self, family, and community" (p. 8).

Epigenetics

The field of genetics is complex: the idea that a single gene controls a specific behavior has been dismissed as researchers now understand that gene networks influence behavior. Things become more convoluted when considering external influences on behavior as current research shows that environmental factors can impact genetic expression. A cell's genetic information is found in DNA, which is packaged into chromatin (Law & Jacobsen, 2010). Epigenetic

modifications of DNA and histones—the core component of chromatin—create an additional layer of information with the ability to influence underlying genetic expression.

Masterpasqua (2009) defines epigenetics as the study of changes in gene expression that remain relatively stable during cell division; epigenetics refers to changes in DNA expression, not variations in DNA sequence. Epigenetics is a biological mechanism for GxE interactions that can be passed transgenerationally whereas other GxE interactions are organism-specific (Dick, 2011). Epigenetics is not a change in genetic inheritance but rather a change in genetic expression (phenotype) (Harper, 2005). Put simply, epigenetics refers to the process by which genetic material is activated or deactivated in varying contexts and situations (Moore, 2015). Moore compares epigenetic modifications of DNA to a dimmer light switch that can be adjusted in various amounts; the activity of a DNA segment, therefore, is dependent on its epigenetic state, which ultimately depends on external factors.

All cells have the same genetic potential (Harper, 2005). Cells differentiate according to external stimuli and can be altered in response to them. This idea is echoed by Masterpasqua (2009) who reports that epigenetic factors controlling gene expression can be influenced by a wide range of factors from hormonal to psychological. Features of the various tissue types are determined by the pattern of gene expression as cells are turned on or off (Harper). The pattern of gene expression, therefore, can be altered as a result of interactions prior to cell differentiation. This process is known as phenotypic plasticity and appears in all forms of life (Weaver, 2007).

A gene is a segment of DNA that gives the cell instructions (Yehuda & Bierer, 2009). The instructions consist of four bases: guanine, cytosine, adenine, and thymine. These bases are repeated in unique sequences that translate into instructions for the cell. According to Harper

(2005), gene expression is controlled by regulating transcription, the process by which DNA is transcribed into messenger RNA (mRNA). Transcription factors within the cell read the instructions and recruit RNA polymerases to copy the DNA through mRNA (Yehuda & Bierer). This process involves more than 100 proteins. As a result, genes can be precisely regulated to not only decide whether a gene product is expressed but also to decide just how much of that product is expressed. Gene regulation does not just occur during transcription, it can also occur before mRNA is translated into proteins or after those proteins have been formed (Masterpasqua, 2009).

DNA methylation. Alterations in gene expression occur by modifying DNA methylation (Lau, 2008). DNA methylation refers to chemical modifications to the chromatin that influence the conformations of chromosomes while influencing the chromatin's interaction with the immediate environment. Essentially, DNA methylation is the process through which gene expression is regulated and is therefore considered an epigenetic mechanism because methylation is impacted by the environment. Epigenetics, therefore, offers a possible mechanistic explanation for the long-term impact the environment has on physiology and behavior (Bird, 2007). DNA methylation is one of many types of epigenetic modifications (e.g., histone acetylation/decetylation) (Yehuda & Bierer, 2009). For the purpose of this paper, DNA methylation will be the central focus as most research on epigenetics is based in this mechanism.

In vertebrates, the methylated sequence is cytosine-guanine (CG) base-pairing (Bird, 2007). Cytosine methylation occurs when a methyl group is added to a certain location of a cytosine base (Yehuda & Bierer, 2009). The CG sequence is paired with an identical sequence on the opposite strand of DNA creating symmetry which means that these sites are briefly methylated on only one of two DNA strands after DNA replication (Bird). These patterns of CG methylation are copied between cell generations. Bird reported that DNA methylation is

associated with stable gene silencing either through interference with the binding of transcription factors or through the recruitment of repressors that specifically bind to sites containing methylated CG. In other words, lasting changes in DNA expression occur when methylation affects transcription factors that in turn affect gene expression which ultimately changes the inherited biological program (Meaney & Szyf, 2005). Methylation has broader implications than epigenetics. For example, methylation can provide insight into the development of cancer as excess methylation can lead to the silencing of tumor suppression genes in carcinogenic cells (Robertson, 2015). With the suppression of these genes, the body is unable to naturally defend itself from the development of all forms of cancer as epigenetic mechanisms influence tumor necrosis factors.

Domestic environmental influence. Domestic environmental influences—the influence of parental behavior and home environment—have been found to cause lasting epigenetic effects on offspring. Domestic environmental influence is largely dependent on the quality and quantity of parental investment (i.e. nutrient supply and behavioral interactions) (Weaver, 2007). According to the attachment theory initially formulated by Bowlby (1969) and later refined by Ainsworth (1979), early behavior and parenting style influences a child's social interactions with others in their lifetimes (see: Simon-Dack & Marmarosh, 2014). Harper (2005) reported it is widely accepted by the scientific community that any event affecting parents may impact their offspring. Furthermore, effects of parenting may not be direct rather as they can be mediated by a child's reaction to them. Variations in parenting may not affect children in the same way, which means that assessment of a child's characteristics is key to understanding how parenting influences offspring. Despite the variations in parental investment, the effects on phenotypic

plasticity are common and often affect the offspring's development of defensive responses and reproductive strategies at a genetic level (Weaver, 2007).

Epigenetics calls for a re-examination of traditional perspectives on genes. It is not so much about what genes a person has but rather about what those genes are doing because any gene has the potential to be "turned off" (Moore, 2015). Methylation, for example, is one way in which genes can be turned off as it leads to gene silencing, which can be passed through cell generations (Bird, 2007). This is crucial as it is the key to recognizing that experience and DNA work together to influence genetic expression. Therefore, human characteristics are not predetermined as the context of a person's life influences who they become. As a result, domestic environmental influences play a key role in genetic expression.

According to Bird (2007), quality of early maternal care can contribute to long-term consequences during the offspring's lifetime. This suggests that the absence of appropriate nurturing results in less methylation which can result in the under-expression of certain neurotransmitter receptors later in life. Champagne (2008) found that decreased maternal care in mice toward a female offspring led to reduced expression of estrogen receptors later in that offspring's life, which further caused lower receptivity of estrogen during the adult offspring's pregnancy. In other words, the adult offspring would release less oxytocin resulting in fewer bonding behaviors toward her own offspring. This can be seen in humans as well when examining socioeconomic stressors and their effects on parental bonding. Socioeconomic stressors (education, income, occupation, etc.) influence the nurturing behaviors of the parents, ultimately leading to the suppression of serotonin, oxytocin, or estrogen receptors in these children (Cacioppo, Tassinary, & Bernston, 2007; Harper, 2005). Behavioral and genetic patterns

like these seem to carry through subsequent generations producing a transgenerational effect on future behavior based on environmental situations the individual has not directly experienced.

The impact of maternal care on genetic expression can be positive as well. Simon-Dack and Marmarosh (2014) provided examples of this. In their review of articles on attachment, they found that mother rats with higher levels of grooming and nursing behaviors have offspring who are less fearful in adulthood, having less severe reactions to stress (Weaver et al. 2004). Due to the increased grooming behaviors, the offspring were found to have increased receptors for oxytocin—a neurotransmitter that regulates stress behavior—in the hippocampus. The increase in the number of receptors allows for the offspring to process more oxytocin ultimately allowing them to better moderate their stress.

Unless one has an identical twin, genetic makeup is unique per individual (Peters, Djurdjinovic, & Baker, 1999). Hans Driesch conducted experiments on sea urchins, separating two cells of a recently divided sea urchin embryo to verify this idea (Moore, 2015). Driesch was testing the current development theory that when a single fertilized egg divides in two, one of the halves was dedicated to the top half of the body while the other was dedicated to the bottom half. This was not what Driesch found, however, as each half became a completely healthy sea urchin. In fact, this is the same process that produces twins and proves that biological outcomes are context dependent. Alignment of particular characteristics in monozygotic and dizygotic twins is one of the most reliable ways of assessing genetic basis (Bird, 2007). Epigeneticists have reported that monozygotic twins do not always show the same disease susceptibility. This suggests that epigenetic differences arise during aging. As a result, while monozygotic twins have the same genetic makeup, the interaction of their genes and their individual environmental contexts (as seen with epigenetics) explains the overall differences between them.

Understanding how epigenetic changes manifest in everyday life is crucial to justifying the need to further study epigenetics. For this paper, domestic environmental influences will be the focus (although there are many other types of environmental influences). As the nature of parental-offspring interaction influences gene expression and behavior development in offspring (Weaver, 2007), domestic environmental influences are crucial to understand. Adversity in the parental environment can alter the nature of the parent-offspring interaction which can then serve as the basis for phenotypic plasticity in the offspring. Autism spectrum disorder (ASD), postpartum depression (PPD), and posttraumatic stress disorder (PTSD) are three prime examples of how domestic environmental influence can result in epigenetic changes.

Autism Spectrum Disorder (ASD)

The prevalence of autism has risen in the United States over the past two decades as our understanding and definition of the disorder have changed. Approximately 147 per 10,000 children are diagnosed with Autism Spectrum Disorder (ASD) by the age of eight (Becerra, et al., 2014). According to Tordjman et al. (2014), ASD is defined as delayed or abnormal functioning in social communication prior to three years of age; it is the manifestation of restricted, repetitive, and stereotyped patterns of behaviors, activities, and interests as seen in the *Diagnostic and Statistical Manual of Mental Disorders V (DSM-V)*. ASD has a psychopathological organization, resulting from effects of various biological and/or psychological factors. Researchers hypothesize that environmental and genetic factors interact to increase the risk of autism development. ASD is thought to be neuro-biologic in origin but the etiology is largely unknown (Lau, 2008). Recent studies emphasize that ASD cannot be explained by a single, biological factor, but rather must be a multifactorial etiology (Tordjman, et al.). Thousands of studies have been conducted with only one commonality: the etiology is

derived from the interaction of genes and the environment (Gentile, et al., 2013). As a result, it is posited that ASD is related to epigenetics.

Bilbo, Jones, and Parker (2012) stated that the epidemiology and genetics of autism are woven together. Furthermore, Bertoglio and Hendren (2009) reported that ASD is thought to involve a complex interaction between multiple and variable susceptibility genes, epigenetic effects, and environmental factors. Autism, therefore, may result when a genetically susceptible child is exposed to an environmental trigger. Because ASD has been found to occur with higher incidence in epigenetic neurodevelopmental disorders, researchers postulate that epigenetics are involved in the pathogenesis of ASD (Lau, 2008).

Researchers have identified more than 200 ASD susceptibility genes, noting that complex patterns of inheritance appear to contribute. As a result, the genetic basis for ASD is well accepted (Bertoglio & Hendren, 2009). Rutter (2011) examined twin and family genetic studies over a period of several decades, consistently finding that ASD has an overall heritability of about 90%. Lau (2008) reported that the 90% heritability drops off rapidly from first- to third-degree relatives. This suggests that ASD is not fully based in genetics as heritability greatly decreases among generations. Furthermore, less than 70% of monozygotic twins are concordant for autism indicating that a certain non-heritable, prenatal, perinatal, or environmental risk factor may exist for ASD. Only about 1% of cases are associated with a rare, pathogenic gene mutation (Rutter), further supporting the large influence the environment has on ASD diagnosis.

As a result of DNA methylation, BCL-2 and retinoic acid-related orphan receptor alpha (RORA) are two candidate genes of ASD that are decreased in the autistic brain (Nguyen, Rauch, Pfeifer, & Hu, 2010). BCL-2 regulates cell death (apoptosis), specifically serving as an anti-apoptotic factor that is important for cell survival during a range of stressful events.

Abnormalities in BCL-2 are correlated with severe mental retardations (Fatemi, Stary, Halt, & Realmuto, 2001). This suggests that dysfunction in apoptotic regulation leads to decreased cognitive function thereby influencing ASD onset. RORA also has many relevant functions related to ASD: regulation of the circadian clock (Akashi & Takumi, 2005), neuroprotection during oxidative stress and inflammation (Boukhtouche, et al., 2006), and cerebellar development, particularly with Purkinje neurons (Gold, Gent, & Hamilton, 2007; Boukhtouche, et al., 2006). Furthermore, increased methylation of MeCP2, another ASD candidate gene, is correlated with gene silencing in the frontal cortex of those with ASD (Nagarajan, Hogart, Gwyne, Martin, & LaSalle, 2006). This further shows how dysregulation of gene expression may result in the pathological symptoms of ASD.

Infections. According to Bertoglio and Hendren (2009), the nature of the environmental trigger is controversial. Environmental factors can be prenatal, perinatal, or postnatal (Tordjman, et al., 2014). Studies have found that ASD may be associated with early exposure to a certain virus (Gentile, et al., 2013). Fetal viral infections are more likely to occur in pregnancy as it is immunosuppressive to prevent the mother's body from rejecting the fetus. As a result, the mother is more susceptible to infections during pregnancy, increasing the fetus's risk of infection. Croen et al. (2005) demonstrated maternal psoriasis, asthma, and allergies diagnosed around the time of pregnancy can be associated with ASD diagnosis in the child. Because the fetus's central nervous system is not fully developed at birth, it is more vulnerable to infection-induced damage (Gentile, et al.). Chess (1971) reported that children diagnosed with congenital rubella syndrome have increased risk of autism. Chess later posited that viral congenital infections in the central nervous system may result in the complex expected symptoms of ASD (Chess, 1977). Viral infections may induce neurological damage through deregulation of the immune system resulting

in autoimmune disturbances (Gentile, et al.). The resulting phenomenon could affect the developing brain by eliciting abnormalities within neural connections by damaging small parts of the myelin sheath on the axon (Singh, 2009; Singh, Warren, Odell, Warren, & Cole, 1993; Singh, 2001; Singh, 2004). These abnormalities may lead to lifelong impairments in higher brain functions like speech, language, communication, and social interaction. Viral infections result from environmental influences and contribute to ASD development as they cause lasting impacts, particularly in influencing the development of the central nervous system. As a result, viral infections are considered an epigenetic mechanism for ASD.

Vitamin deficiencies. Due to the fact that ASD diagnoses have increased in the past few decades and the idea that environmental factors also contribute to the diagnosis, it is important to determine what medical conditions have increased in the last few decades that could link infections, immune deregulation, and ASD together. According to Gentile et al. (2013), vitamin D deficiency is one possible answer. As a result of lifestyle modifications, the prevalence of vitamin D deficiency has risen in the past decades. Vitamin D is seldom found in food so it is mainly synthesized through ultraviolet radiation. Pregnant women are more likely to have vitamin D deficiency because they are often instructed to avoid direct sunlight. Vitamin D regulates calcium metabolism, serves as a switch that activates over 200 genes, and controls the immune response. Research has shown that vitamin D deficiency in early life affects neuronal differentiation and axonal connectivity thereby impacting brain structure and function (Kocovska, Fernell, Billstedt, Minnis, & Gillberg, 2012; Eyles, Burne, & McGarh, 2012).

High prevalence of vitamin D deficiency has been reported in non-Western immigrants (Fernell, et al., 2009). Fernell et al. conducted a study in Stockholm County to analyze vitamin D levels of mothers of Somali origin and mothers of Swedish origin who have children with and

without autism. Women of Somali origin had significantly lower values of vitamin D. Furthermore, mothers of Somali origin with autistic children had approximately 30% lower mean values of vitamin D compared to mothers of Somali origin with non-autistic children. Although the sample size was relatively low, the study suggests that further research is necessary into the impact vitamin D has on brain development.

Maternal folic acid deficiencies have also been prevalent in the development of ASD. Folic acid is essential for basic cellular processes such as DNA replication and protein methylation (Neggers, 2014). Folic acid is crucial during development of the neural tube (the embryonic cells that become the central nervous system). Research shows that the time period in which the neural tube closes overlaps with the time in neurogenesis that is critical for ASD development (Rogers, 2008; Rodier, Ingram, & Tisdale, 1996; Haggerty, et al., 2008). If folic acid is lacking during development, improper neural tube closure can lead to issues such as ASD. Many studies report that the use of prenatal folic acid supplements decreases the risk of ASD in offspring (Schmidt, et al., 2012; Schmidt, et al., 2011; James, et al. 2010). Suren, et al. (2013) evaluated 85,176 children from the Norwegian Mother and Child Cohort Study, reporting that ASD occurred in half as many offspring whose mothers took folic acid supplements compared to offspring whose mothers did not. Based upon this, folic acid deficiency is thought to contribute to ASD development, but more research needs to be done to understand the extent in which folic acid influences ASD development. As vitamin D and folic acid deficiencies result from environmental influences and causes lasting changes in brain structure and immune response, they are considered an epigenetic mechanism for ASD.

Maternal birth abroad. Given the results of Fernell et al. (2009), ASD may also be linked to race/ethnicity and immigration. Autism phenotype differences related to intellectual

and language disabilities across race/ethnic groups in the United States suggest differences in ASD etiology and disparities in diagnostic and treatment-related factors (Pedersen, et al., 2012; Cuccaro, et al., 2007; Chaidez, Hansen, & Hertz-Picciotto, 2012; Jarquin, Wiggins, Schieve, & Van Naarden-Braun, 2011). Beccerra et al. (2014) investigated the influence of maternal race/ethnicity and nativity on ASD diagnosis in LA County, California. They found evidence that children of foreign-born Black, Filipino, and Vietnamese mothers had higher risks of developing or being diagnosed with ASD compared to children of white US-born children. Foreign-born black mothers were reported to have the highest risk of bearing children with ASD. These findings suggest the environment is critical in shaping the phenotype.

Gardener, Spiegelman, and Buka (2009) conducted a meta-analysis, reporting that children of mothers born abroad had increased risk of being diagnosed with autism. Results were especially strong in Nordic countries, where maternal immigration resulted in a large increase in the risk of autism diagnosis among the mother's children. Furthermore, Dealberto (2011) found increased risk of autism diagnosis in children whose mothers were born abroad; this increase was seen in Europe, North America, and Australia. Dealberto reported that the risk varied depending on ethnicity and noted that offspring of dark skinned migrants were especially at risk. One well-received theory suggests that mothers born abroad may not receive the proper immunizations putting them more at risk for innocuous infections. Other researchers believe that the social and economic stressors a mother experiences in a new country can impact the well-being of her offspring (Becerra, et al., 2014). More research needs to be conducted to explore what specific factors relate to this, but evidence suggests it may be unique based upon the culture as well as the genetic variation among race/ethnicity. For example, a large portion of Filipino mothers are employed in healthcare which increases their risk of exposure to infections (Beccerra, et al.).

Based on the research of Gentile, et al. (2013), a mother's exposure to infection can increase the risk of a fetal infection.

Given the research on infections, vitamin deficiencies, and maternal birth abroad coupled with over 200 ASD susceptible genes, it can be concluded that ASD results from the interaction of genetics and external factors, rather than genetics alone (see *Figure 1*). As a result, epigenetic factors likely contribute to the development ASD. Understanding the interaction of genes and environment provides insight into ASD etiology and is crucial to developing treatment options for those with ASD especially given the variability of the spectrum with the updated definition in the *DSM-V*. Striving to understand the specific interaction of genetic and external factors in each individual could lead to the development of an individualized treatment plan catered to the individual's case.

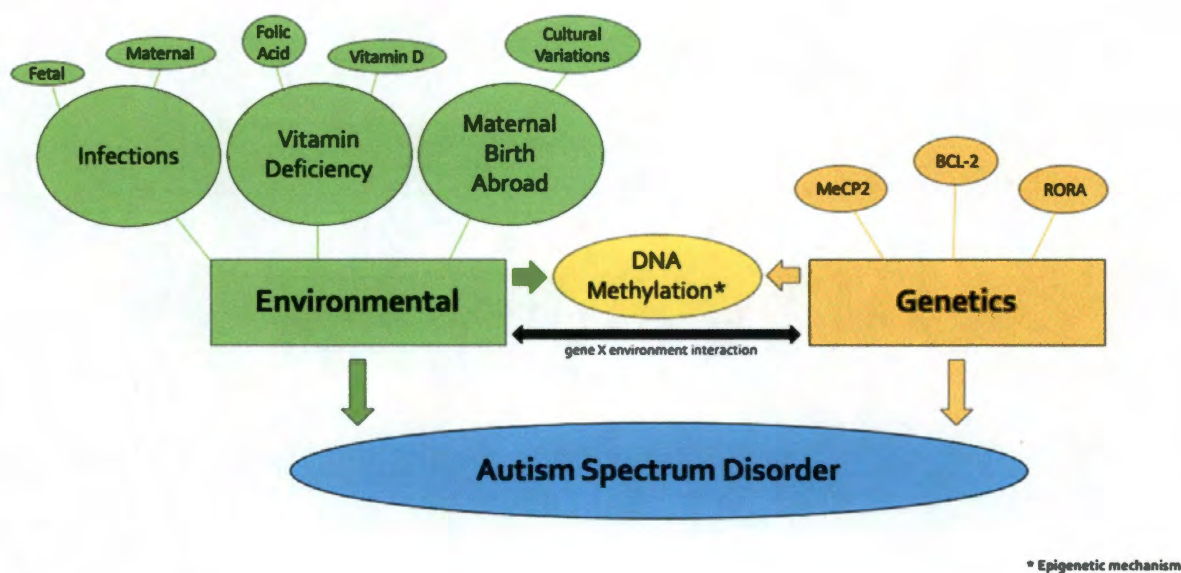


Figure 1. Interaction of genetic and environmental factors in ASD.

Postpartum Depression (PPD)

Postpartum depression (PPD) is a serious condition defined by moderate to severe depression after the birth of a child, which can occur in both the mother and father (Don & Mickelson, 2012). The *DSM-V* does not recognize PPD as its own separate disorder; rather it is classified under “Major Depressive Disorder (MDD) with Peripartum Onset” (American Psychiatric Association, 2013). As such, PPD symptomology matches that of depression (i.e. agitation/irritability, change in appetite and sleep, anxiety, loss of energy, concentration, and interest). For this paper therefore, PPD will be examined through MDD etiology. Review of recent research suggests that both genetic and environmental factors contribute to the diagnosis of MDD. According to Cicchetti and Toth (1998), biological, social, and psychological systems must be evaluated across development as one risk factor alone rarely results in depression. “Depression disorders are of particular interest because of the complex interplay of psychological (e.g. affective, cognitive, socioemotional, social-cognitive), social (e.g. community, culture), and biological (e.g. genetic, neurobiological, neuropsychological, neurochemical, neuroendocrine) components that are involved” (Cicchetti & Toth, 1998, p. 224). As a result, it is posited that PPD is related to epigenetics.

According to Weissman, Leaf, and Tischler (1988), 30% of depression in women occurs with reproduction-related life events. Specifically, the risk of women developing psychiatric disorders increases during the postpartum period (Hopkins, Marcus, & Campbell, 1984). Within adults, depressive disorders have been found to coincide with other disorders such as anxiety, substance abuse, and schizophrenia (Cicchetti & Toth, 1998). Research has shown that 80% of cases of PPD go undetected and untreated (Gise, 1992). Understanding PPD etiology is important as research indicates that history of PPD significantly increases the odds of mothers

using corporal punishment on their children (Knox, Rosenberger, Sarwar, Mangewala, & Klag, 2015). Furthermore, recent studies have explored how societal constructs of the “baby blues” can influence a woman’s chance of developing PPD (Held & Rutherford, 2012). Although depression is preventable and treatable, many still forego treatment as a result of stigmas associated with the disorder (Cicchetti & Toth, 1998). Understanding how genetics and the environment interact to influence depression will allow researchers to start prevention efforts earlier to minimize the risk of developing the disorder.

Kaminsky and Payne (2014) identified biomarkers for PPD that allowed researchers to identify whether a woman would experience PPD or not, regardless of the woman experiencing depression during pregnancy or not. The molecular changes exhibited by the biomarkers may indicated a biological vulnerability to PPD. These changes may then interact with environmental stressors during the postnatal period and could ultimately lead to depression (Kaminsky & Payne). Furthermore, their research suggests that women at risk for PPD are more likely to have estrogen-based DNA methylation.

Research strongly supports the genetic link to the development of depression as depression often runs in families (Cicchetti & Toth, 1998). A glucocorticoid receptor (GR), also known as the NR3C1, is a crucial binding site for cortisol and other glucocorticoids (steroid hormones). As a major component of the endocrine system, GRs influence stress response. Specifically with MDD, the hypothalamic-pituitary-adrenal (HPA) axis is one of the major neuroendocrine systems involved in short-term responses to stress (Yehuda & Bierer, 2009). The HPA regulates digestion, immune system function, and mood and emotions as well. Methylation of GR can influence the HPA, increasing the likelihood of MDD. Radley et al. (2011) reported that 80% of patients with MDD show increased HPA activation. Increased HPA activation

results in higher levels of daily cortisol release which promotes the feeling of stress. This, in turn, can lead to depression.

There is more to MDD and PPD than genetics, however. Twin studies found that the heritability of severe and moderate depression is moderate (Kendler, Neale, Kessler, Heath, & Eaves, 1992). Rende et al. (1993) investigated how genetic and environmental factors contribute to symptoms of depression in adolescents participating in a combined twin and stepfamily study. They reported that genetics had a moderate influence on the range of individual differences in symptomology. Furthermore, Rende et al. reported a nonsignificant genetic influence and a significant shared environmental influence on severe depression. These results suggest that environmental factors must be considered when understanding the etiology of depression.

Social support. Social support is a key environmental factor in PPD. Don and Mickelson (2012) found an indirect relationship between maternal and paternal PPD through reports of impaired spousal support and low relationship satisfaction. One of the biggest indicators of maternal and paternal PPD is quality of the spousal relationship. Social support research suggest that the quality of social support is dependent upon the presence (or absence) of a supporter rather than the amount of support being given (Hobfoll, Ritter, Lavin, Hulsizer, & Cameron, 1995). Studies have shown that pregnancy and postpartum periods are often characterized by a decline in relationship adjustment (Carter, Grigoriadis, & Ross, 2010; Whisman, Davila, & Goodman, 2011). Don and Mickelson reported that maternal PPD is related to increased negative interactions with and less social support from the spouse. Women who experienced PPD reported high incidents of intimate partner violence prior to and during their pregnancy (Flanagan, Gordon, Moore, & Stuart, 2015).

Socioeconomic status. Hobfoll et al. (1995) found that a significant association between low socioeconomic status (SES) and PPD, finding depression rates twice as high compared to women in the middle-class. They further found that other demographic factors (like ethnic status) had no effect on PPD suggesting that poverty (low SES) is a primary factor in influencing depression. Low SES in women is associated with more frequent exposure to chronic life stressors (Dohrenwend & Dohrenwend, 1981; Kessler et al., 1994) suggesting increased HPA activation among those in poverty. As impoverished mothers have less control over the frequency of stressors, they are more susceptible to experience negative effects as a result of stressors. Their increased vulnerability to chronic stress stems from increased responsibilities in raising while also having to cope with chronic helplessness, hopelessness, alienation, and marginalization.

Societal constructs. Held and Rutherford (2012) reported that societal constructs of the “baby blues” can influence the development of PPD. As early as the 1950s, portrayals of postpartum life began to appear in popular magazines. With this, mass media became the central reference for mothers on childrearing. While the portrayal of the motherhood-mood relationship varied across media, all depictions did not accurately represent the complexity of the relationship (Held & Rutherford). The development of “motherhood mystique” only increased the pressure on women to have a strong bond with their child (Macdonald, 2013). Within this ideology, mothers are told that they should be home with their children in the early years in order for them to develop properly. Having to place a child in daycare, then, can cause the mother to have extreme guilt, which can lead to feelings of depression. PPD has also been shaped by many factors (i.e. medicalization of childbirth, influence of male experts, advent of psychopharmaceuticals, second-wave feminism, etc.), but the overall message the media

portrayed was the negative emotions as a result of motherhood indicate something wrong with the mother herself rather than motherhood in general. This indicates that society plays a large part in the onset of PPD by stigmatizing depression as a result of childbirth. The above environmental factors are extremely influential in the development of PPD because they directly influence the way genes are expressed and are therefore considered an epigenetic mechanism for PPD.

Given the research on social support (Don & Mickelson, 2012), SES (Hobfoll, Ritter, Lavin, Hulsizer, & Cameron, 1995) and societal constructs (Held & Rutherford, 2012) coupled with the genetic biomarkers found for PPD (Kaminsky & Payne, 2014), it can be concluded that PPD results from an interaction of genetics and environmental factors (see *Figure 2*). This suggests that epigenetic factors influence the diagnosis of PPD. Understanding this is crucial because researchers have found that PPD increases the likelihood of corporal punishment and neglect (Knox, Rosenberger, Sarwar, Mangewala, & Klag, 2015). Other research has shown that PPD has profound impacts on the mental well-being of the child. This can cause depression-like brain readings in the infants as PPD often results in impaired parent-infant bonding resulting long-term consequences on the offspring's health (Center on the Developing Child at Harvard University, 2009). Recognizing the impact environmental influences have on PPD in addition to the genetic factors will allow clinicians to develop interventions sooner so as to prevent the onset of PPD later. Early intervention will not only ensure the health and wellbeing of the parents but also that of the offspring. As depression is treatable, the damage to children can be prevented.

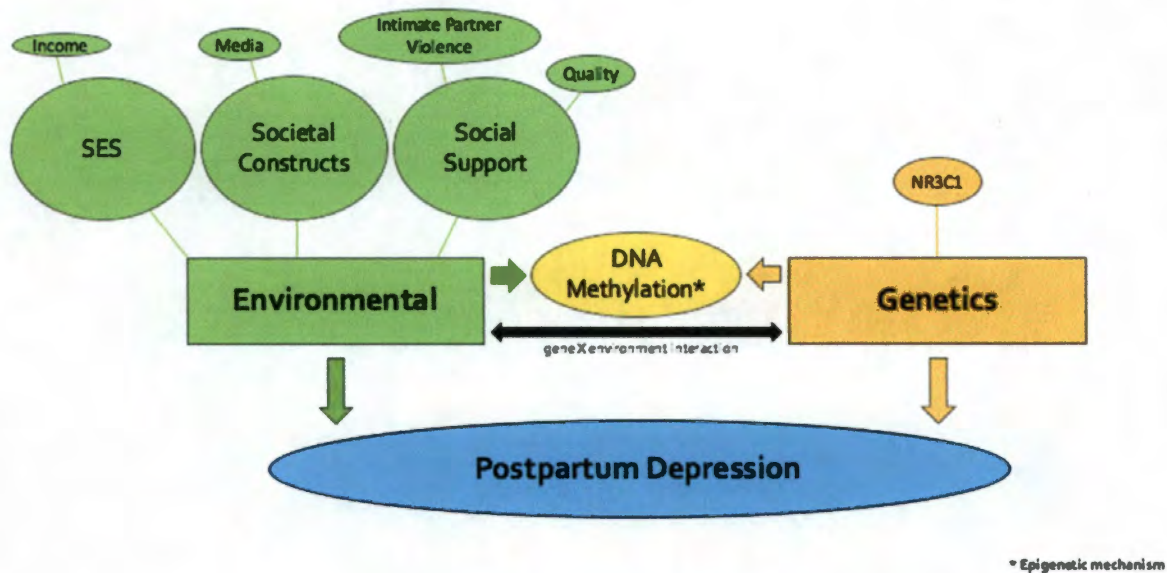


Figure 2. Interaction of genetic and environmental factors in PPD.

Posttraumatic Stress Disorder (PTSD)

Posttraumatic stress disorder (PTSD) occurs after an individual is exposed to a traumatizing experience such as death, serious injury, or sexual violence (American Psychiatric Association, 2013). According to the *DSM-V*, individuals can experience trauma in one of four ways: direct trauma, indirect trauma, repeated exposure, and learning a traumatic event happened to a loved one. Individuals experiencing PTSD often have recurrent and distressing memories and/or dreams of the event, flashbacks, intense psychological distress, and often avoid stimuli that are associated with the event. Research has shown, however, that there are numerous individual differences in symptomology after exposure to trauma (Yehuda & Bierer, 2009). As such, it is important to consider environmental and biological factors in PTSD.

Recent research in PTSD has focused on genetic factors that may increase the risk for environmental exposures through the behavior of caretakers (Kendler & Baker, 2007; Scarr & McCartney, 1983). Kendler and Baker found evidence that certain heritable traits (like

impulsivity, aggression, and substance abuse) may influence an individual's decision to be in a potentially adverse environment. Furthermore, genes can impact how an individual responds to specific environmental events (Obradovic & Boyce, 2009). The strongest evidence supporting an association between genetics and PTSD has been shown in the higher similarity in rates of PTSD in monozygotic twins compared to dizygotic twins (Yehuda, et al., 2010).

While much research has shown that PTSD can occur in an individual with history of early traumatization, it is possible to develop PTSD without early traumatization (Yehuda, et al., 2010). True et al. (1993) first showed this in a study of combat veterans, suggesting that genetic factors contributed to the development of PTSD symptoms by influencing biological mechanisms associated with stress response. More recent research in twins shows that 38% of variability in PTSD symptoms is related to genetic factors. Additionally, authors found a common genetic basis for PTSD and exposure to assault (non-combative) suggesting that personality traits such as anger and irritability can increase one's likelihood of being exposed to assault (Stein, Jang, Taylor, Vernon, & Livesley, 2002). For example, someone with high irritability is more likely to be involved in physical assault than someone with low irritability.

Similar to PPD, methylation of GR gene (NR3C1) has been shown to increase GR sensitivity thereby increasing one's likelihood of developing PTSD (Yehuda, et al., 2014; Yehuda, et al., 2015). Another gene of interest in PTSD is FKBP5 (Yehuda, et al., 2010). FKBP5 is a stress-related gene that regulates cortisol's ability to bind to GRs; over-activity decreases cortisol binding while under-activity increases cortisol binding. Binder et al. (2008) conducted a study with 700 adults seeking medical care, focusing on eight single nucleotide polymorphisms (SNPs) of the FKBP5 gene in association with adult PTSD. Four SNPs within FKBP5 were found to interact with the severity of childhood trauma to predict the severity of adult PTSD. In

other words, people exposed to severe trauma as a child are more susceptible to developing severe PTSD later in life. Because not everyone exposed to trauma develops PTSD (and trauma exposure is necessary for a PTSD diagnosis according to the *DSM-V*), genetic factors are not the only cause for PTSD; environmental factors must also be considered.

Non-normative experiences. Like PPD, PTSD is influenced by alterations in the HPA axis. Francis and Meaney (1999) observed that differences in early rearing of rat pups can recalibrate the HPA axis. This research provided a paradigm for how the environment can produce lasting modifications to the HPA axis in humans (Yehuda & Bierer, 2009). Researchers produced phenotypic difference in maternal behavior by handling postpartum mother rats for 15 minutes over several days before returning them to their pups (Liu, et al., 1997). The mothers that were handled showed increased licking and grooming behaviors. The pups of the handled mothers had lower cortisol levels and more GR responsiveness in adulthood compared to the pups of non-handled mothers. This shows how early environmental influences (like maternal behavior) can interact with gene expression to influence behaviors in times of stress. These results were further supported in a longitudinal study of adopted children which found that over-reactive maternal parenting style predicted lower cortisol variability in offspring whereas a similar paternal parenting style predicted higher cortisol variability (Marceau, et al., 2013). This supports the idea that non-normative, not necessarily traumatic events (like parental attachment and parenting style) can increase an offspring's likelihood of developing PTSD as it impacts GR programming (Yehuda, et al., 2010).

Indirect trauma. Research shows that offspring of trauma survivors are more susceptible to developing mental and physical illnesses (Palosaari, Punamaki, Qouta, & Diab, 2013; Field, Om, Kim, & Vorn, 2011; Yehuda, Schmeidler, Wainberg, Binder-Brynes, & Duvdevani, 1998).

Much research has been conducted on Holocaust survivors with PTSD and their offspring. Maternal PTSD has been associated with higher susceptibility of the offspring in the development of PTSD whereas paternal PTSD was associated with the increased susceptibility to MDD. Maternal PTSD was also found to be more strongly associated with lower cortisol levels compared to paternal PTSD (Yehuda & Bierer, 2008). Lower cortisol levels were also found in offspring of women who were pregnant and developed PTSD after exposure to the World Trade Center attacks on September 11, 2001 (Yehuda, et al., 2005).

Research has found that PTSD in both parents results in an offspring phenotype, which includes lower GR methylation, ultimately resembling PTSD (Yehuda, 2002; Yehuda, et al., 2015). It is posited that because both parents are traumatized, the child repeatedly experiences unpredictable parental behavior that causes hyper-vigilance in the offspring. Furthermore, PTSD in one parent may mediate the parenting style of the other, ultimately altering the family environment as Lehrner, et al. (2014) reports that paternal PTSD is associated with high levels of family conflict.

Direct trauma. Yehuda, et al. (2014) conducted a study on 122 combat veterans, 61 with PTSD and 61 without PTSD, to examine methylation of NR3C1 (GR gene) and three other neuroendocrine markers of the HPA on PTSD diagnosis. Researchers found significantly lower levels of NR3C1 methylation in trauma-exposed PTSD veterans compared to those with similar trauma exposure and no PTSD. This supports the idea that epigenetics influences the development of PTSD as lower methylation of NR3C1 is a key factor in PTSD development. Furthermore, lower FKBP5 gene expression has been found in PTSD patients contributing to altered neuroendocrine measures associated HPA activity in PTSD patients (Segman, et al., 2005; Sarapas, et al., 2011; Yehuda, et al., 2009).

Given the research on non-normative experiences, indirect trauma, and direct trauma, as well as the implications these have on NR3C1 and FKBP5, it can be concluded that PTSD can be result of epigenetics (see *Figure 3*). Understanding this is crucial to developing individualized treatments for those with PTSD; by understanding the specific environmental and genetic factors that are implicated in their diagnosis, clinicians can customize treatment plans to accommodate for the patient's unique gene and environment interactions. As much research on PTSD shows, offspring of trauma survivors (especially those survivors with PTSD) can develop physical and mental illnesses (Palosaari, Punamaki, Qouta, & Diab, 2013; Field, Om, Kim, & Vorn, 2011; Yehuda, Schmeidler, Wainberg, Binder-Brynes, & Duvdevani, 1998). Focusing on the individualized treatment of PTSD can ensure the mental and physical health of the trauma survivor as well as their offspring.

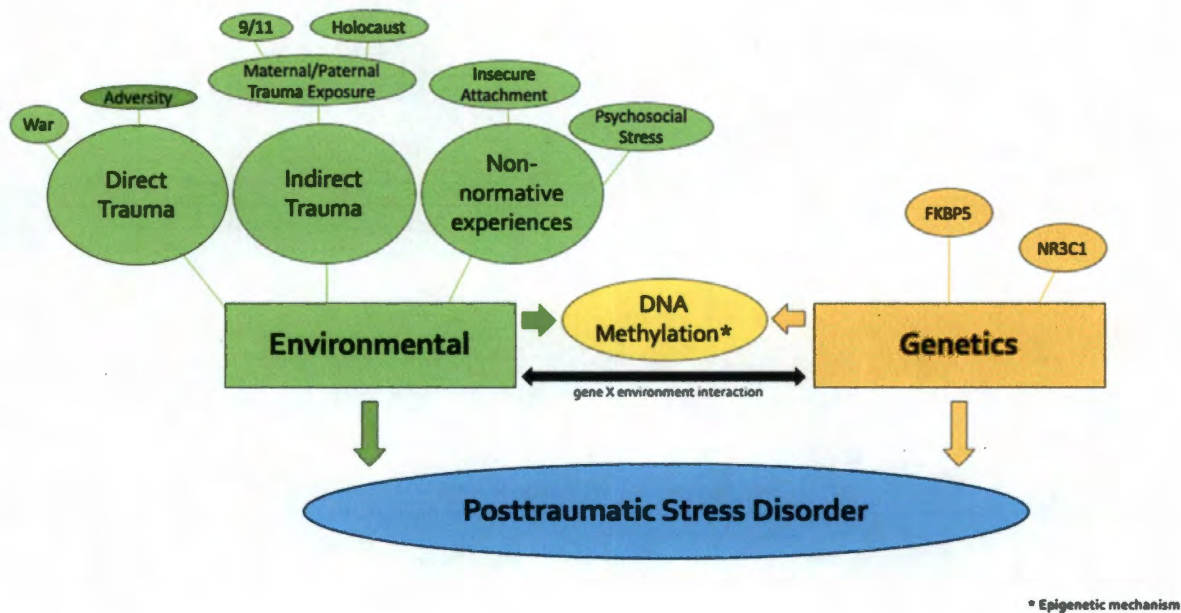


Figure 3. Interaction of genetic and environmental factors in PTSD.

Discussion

The current review explored epigenetics, examining the crucial role the environment plays in mediating genetic effects on behavior as epigenetics is a biological mechanism of gene by environmental interactions. Epigenetics was examined with respect to three different mental disorders: ASD, PPD, and PTSD. The purpose of this review was to justify the need to study epigenetics and to propose ideas for future areas of research within the field. While there are many epigenetic mechanisms, DNA methylation was the primary focus of this paper as most research on epigenetics is based on this mechanism. Furthermore, while there are many environmental influences, the main focus of this paper was domestic environmental influences as parental environment has lasting impacts on the development of children.

Autism spectrum disorder. ASD is a complex disorder impacted by gene and environment interaction. Vitamin deficiencies, viral infections, and maternal birth abroad are three prominent environmental influences that contribute to methylation of key genes associated with ASD diagnosis: MeCP2, BCL-2, and RORA. RORA influences cerebellar development, the circadian clock, and neuroprotection during stress. BCL-2 regulates cell death (apoptosis) as an anti-apoptotic factor. Abnormalities with BCL-2 have been shown to lead to severe mental retardation, decreasing cognitive function thereby influencing ASD development. Dysregulation of MeCP2 is correlated with gene silencing in the frontal cortex further decreasing cognitive function of those with ASD.

Postpartum depression. PPD results from the interaction of genes and the environment. Low SES, societal constructs, and spousal support are three environmental influences that impact methylation of NR3C1, a key gene associated with PPD development. NR3C1 is a glucocorticoid receptor (GR) promoter which influences stress response as mediated by the

hypothalamic-pituitary-adrenal axis (HPA). Increased HPA activation results in higher levels of daily cortisol release, promoting increased feelings of stress which can ultimately lead to depression.

Posttraumatic stress disorder. PTSD also results from gene and environmental interactions. Direct trauma, indirect trauma, and non-normative experiences are key environmental influences that impact the methylation of prominent genes associated with PTSD: FKBP5 and NR3C1. NR3C1 is GR promoter which influences stress response as mediated by the HPA while FKBP5 regulates cortisol's ability to bind to GRs. Increased HPA activity can result in higher levels of cortisol, influencing a person's susceptibility to developing PTSD.

Epigenetics is important to study as it demonstrates the role the environment plays in mediating behaviors through the alteration of genetic expression. The role of the environment is often acknowledged when studying mental disorders but the true extent of its influence is generally overlooked as the biological and genetic side of psychology is often disregarded. Diagnosis and counseling of mental disorders is based on subjective information, founded in the symptoms and emotions expressed by the individual as the genetic and biological correlates are not directly assessed by clinicians. As we further understand epigenetics, we can work to integrate these methods into the diagnosis of mental disorders to more accurately diagnosis disorders and better treat individuals based on their current circumstances.

Implications and Future Research

The current review raises numerous implications. The way we educate others about ASD, PPD, and PTSD needs to be more interdisciplinary as this review demonstrates that numerous factors influence the development of psychological disorders, specifically through GxE interactions. Education on these areas should incorporate a broad range of topics along with

psychology such as biology, genetics, and sociology. Education should further emphasize the complex nature of the effect genes have on behavior to better demonstrate how influential environmental stimuli can be.

Clinicians can also derive many implications from this review. By understanding an individual's specific environmental and genetic factors, clinicians can develop specialized treatment plans catered to the specific needs of their client. Through this, clinicians can ideally limit the onset and severity of disorders like PPD and PTSD. ASD may be more challenging to prevent, but its severity can definitely be limited by specialized treatments. More work needs to be done to understand the extent of environmental influences as well as genetic factors. Additionally, more research should examine the role of neurotransmitter systems and epigenetics in these disorders to influence development of psychopharmaceuticals.

Of the numerous environmental influences, the main focus of this review was domestic environmental factors, demonstrating the crucial role parental and home environment plays in development. Parents are not to blame for their children coming to develop a mental disorder because how the environment and genetics will interact to influence epigenetic expression is well beyond any person's ability to predict. Furthermore, environmental factors like low SES and birth abroad are not always controllable. As a result, parents should not be blamed for any issues their child develops. Parents should, however, be aware of the impact their genes and environment have on their offspring, acknowledging that many uncontrollable environmental factors also contribute to offspring development.

Future research should examine the transgenerational impact of epigenetic modifications to DNA to understand if they are permanent or reversible on an individual and generational level. Current research suggests that epigenetic changes may not be permanent if the environmental

stressor that caused the methylation is no longer present. In other words, epigenetic changes may revert back to their original state in the absence of the stimulus that influenced methylation in the first place. More research needs to be done to verify this, however. Research should also investigate the long-term impacts of methylation if the environmental stressor continues to be present to understand how epigenetic changes are passed transgenerationally. Additionally, researchers need to determine if there are epigenetic mechanisms beyond DNA methylation and histone acetylation/decetylation; while it is thought there are more, these are the most defined and well-known epigenetic mechanisms. This would provide insight into the extent that epigenetic modifications have in everyday life.

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